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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,922	05/10/2001	Toshihiro Kuroita	10089/14	5846

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EXAMINER

HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 12/27/2002

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/852,922

Applicant(s)

KUROITA ET AL.

Examiner

Richard G Hutson

Art Unit

1652

-- The MAILING DATE of this communication appears in the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) 13-24 and 29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12, 25-28 and 30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 May 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4, 5.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Applicants preliminary amendment of claims 17, 19, 22, 26-30 and 20, Paper No. 8, 5/10/2001, is acknowledged. Claims 1-30 are still at issue and are present for examination.

Election/Restrictions

Applicant's election of Group I, Claims 1-12, 25-28 and 30, in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 13-24, and 29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

Applicants claim of the benefit of foreign application JAPAN 2000-138796, filed 5/11/2000, is acknowledged. It is noted that a certified copy of application JAPAN 2000-138796 has been received.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other

Art Unit: 1652

information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosures, Paper No. 4, filed 8/9/2001, and Paper No. 5, filed 10/16/2001, is acknowledged. Those references considered have been initialed. Reference, Kong et al., IDS Paper No. 5, is a duplicate of a reference listed in Paper No. 4 and has been lined through. Reference Japan 05-328969 was not found in the application file and has therefore not been considered.

Drawings

The drawings filed on 5/10/2001 are accepted and have been approved by the draftsman.

Specification

The disclosure is objected to because of the following informalities:

On page 1, lines 13, applicants misspell "recent" as "resent".

The application lists the description of the figures on page 59, just prior to the claims. It is suggested that this be moved forward in the application closer to the beginning of the application.

It is noted on page 38, that applicants refer to "Reference Example 1" and on page 40 applicants refer to "Example 1". The distinction between "Reference Example 1" and "Example 1" is unclear and deserving of comment.

Art Unit: 1652

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth: Figure 1 lists 6 sequences, none of which appear to have associated sequence identifiers. Further it is noted that these sequences depicted in the figures should have sequence identifiers in the figure or in the description of the figure.

Appropriate correction is required.

Claim Objections

Claims 1 is objected to because of the following informalities:

Claims 1 recites "the EXO I region". It is suggested that applicants amend this recitation to "the exonuclease I region".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 25-28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (claims 2-12, 25-28 and 30 dependent on) is indefinite in that language used is repetitive and thus unclear. Claim 1 recites "A modified thermostable DNA polymerase wherein in the DX₁EX₂X₃X₄H sequence (D: aspartic acid, E: glutamic acid, H: histidine, X₁, X₂, X₃, and X₄: any amino acid) consisting of DX₁E sequence within the EXO I region and a four amino acid length peptide adjacent to said glutamic acid (E) of thermostable DNA polymerase having 3'-5' exonuclease activity, histidine (H) has been replaced by another amino acid." The limitation "...consisting of DX₁E sequence within the EXO I region and a four amino acid length peptide adjacent to said glutamic acid (E).." is confusing because it is unclear what this adds to the claim, as this appears to only repeat the earlier reference to "the DX₁EX₂X₃X₄H sequence (D: aspartic acid, E: glutamic acid, H: histidine, X₁, X₂, X₃, and X₄: any amino acid)". An amendment such as the following would help applicants overcome this rejection. For the purpose of advancing prosecution, the claim is interpreted as "A modified thermostable DNA polymerase having 3'-5' exonuclease activity, wherein in the DX₁EX₂X₃X₄H sequence (D: aspartic acid, E: glutamic acid, H: histidine, X₁, X₂, X₃, and X₄: any amino acid) within the exonuclease I region of the thermostable DNA polymerase, histidine (H) has been replaced by another amino acid."

Claim 4-5 (Claims 6-12, 25-28 and 30 dependent on) recite the limitation " in the DIETLYH sequence (D: aspartic acid, I: isoleucine, E: glutamic acid, T: threonine,, L: leucine, Y: tyrosine, H: histidine) located at the 141-147-positions in the amino acid sequence of SEQ ID NO: 2," in the modified thermostable DNA polymerase according to claim 3. There is insufficient antecedent basis for this limitation in the claims from

Art Unit: 1652

which these claims depend (i.e. claim 3). It is realized that the DIETLYH sequence is encompassed within those modified polymerases, comprising the DX₁EX₂X₃X₄H sequence, claimed in claim 3, however the reference to the specific sequence "DIETLYH" is unclear.

Further as the only difference between claims 4 and 5, and claim 3, from which claims 4 and 5 depend, is the increased DNA extension rate (i.e. 30 or 40 vs. 20 bases/second) and increased thermostability (i.e. 40% or 60% vs. 10%), the recited physicochemical property (3) is interpreted as the amino acid sequence of the claimed modified thermostable DNA polymerase comprises SEQ ID NO: 2, wherein the histidine in the DIETLYH sequence at positions 141 to 147 of SEQ ID NO: 2, has been replaced with another amino acid.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 25-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 25-28 and 30 are directed to all possible modified thermostable DNA polymerases having 3'-5' exonuclease activity, wherein in the DX₁EX₂X₃X₄H sequence within the EXO I region of the thermostable DNA polymerase, histidine (H) has been

Art Unit: 1652

replaced by another amino acid and reagent kits and compositions comprising said modified thermostable DNA polymerase. The specification, however, only provides the those representative species having the sequence of SEQ ID NO: 2 encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these modified thermostable polymerases by any identifying structural characteristics or properties other than the activities recited in claims 1-3, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. It is noted that claims 4-12 have not been included in this rejection based on the above discussed (See 112 2nd paragraph rejection) interpretation of physicochemical property (3) of claims 4 and 5.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-3, 25-28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified thermostable DNA polymerase having 3'-5' exonuclease activity, comprising SEQ ID NO: 2, wherein the histidine in the DIETLYH sequence at position 141 to 147 of SEQ ID NO: 2, has been

Art Unit: 1652

replaced with another amino acid., does not reasonably provide enablement for **any** modified thermostable DNA polymerase having 3'-5' exonuclease activity, wherein in the DX₁EX₂X₃X₄H sequence within the EXO I region of the thermostable DNA polymerase, histidine (H) has been replaced by another amino acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3, 25-28 and 30 are so broad as to encompass any modified thermostable DNA polymerase having 3'-5' exonuclease activity, wherein in the DX₁EX₂X₃X₄H sequence within the EXO I region of the thermostable DNA polymerase, histidine (H) has been replaced by another amino acid and reagent kits and compositions comprising said modified thermostable DNA polymerase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of modified thermostable DNA polymerases broadly encompassed by the claims, including all of those thermostable DNA

polymerases currently known as well as those yet to be discovered. The claims rejected under this section of U.S.C. 112, first paragraph, place minor structural limits on the claimed enzymes. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the modified thermostable DNA polymerase comprising SEQ ID NO: 2, wherein the histidine in the DIETLYH sequence at positions 141 to 147 of SEQ ID NO: 2, has been replaced with glutamic acid, aspartic acid, tyrosine, alanine, lysine, arginine, serine or glutamine.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any modified thermostable DNA

Art Unit: 1652

polymerase, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting polymerase/exonuclease activity; (B) the general tolerance of thermostable polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a thermostable DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain polymerase/exonuclease activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the claimed polymerase activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any thermostable polymerase. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is

unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Remarks

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read 'Richard Hutson', with a long horizontal line extending to the right.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
December 27, 2002